Introduction to Carbapenem-Resistant Enterobacteriaceae (CRE)

Keith S. Kaye, MD, MPH
Professor of Medicine, Wayne State University
Corporate Vice President, Quality and Patient Safety
Corporate Medical Director, Infection Prevention, Hospital Epidemiology and Antimicrobial Stewardship
Detroit Medical Center
Detroit, MI

Overview

- Epidemiology of CRE
- Treatment options for CRE
- Control of CRE

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

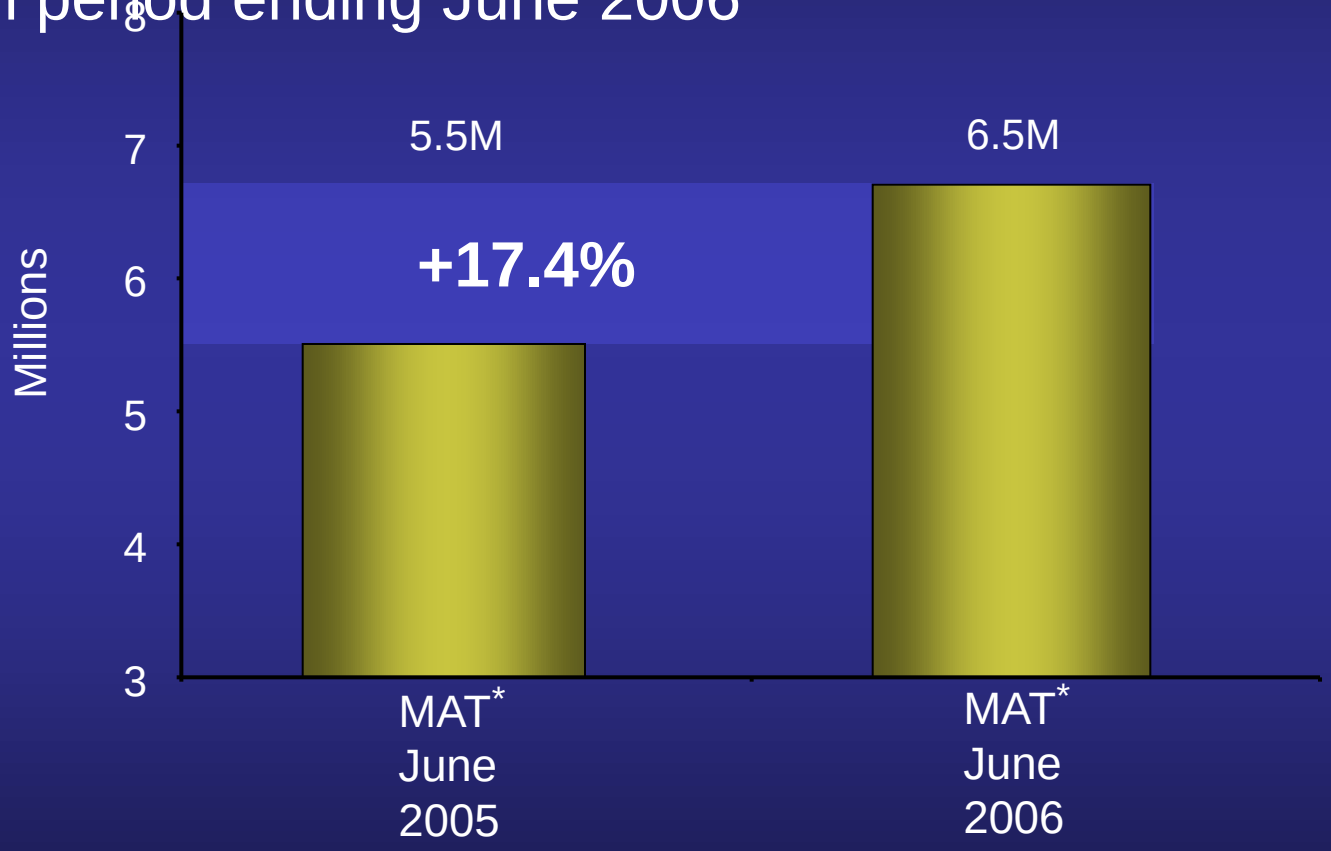
Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

- Bad Bugs, No Drugs: No ESKAPE
  - *Enterococcus faecium* (E), *Staphylococcus aureus* (S), *Klebsiella pneumoniae* (K), *Acinetobacter baumannii* (A), *Pseudomonas aeruginosa* (P), and *Enterobacter* spp. (E)
- The late-stage clinical development pipeline remains unacceptably lean
  - Some important molecules for problematic pathogens such as MRSA
  - Few novel molecules for other ESKAPE pathogens
  - No new drugs for infection due to multidrug-resistant Gram-negative bacilli (eg, *A. baumannii* and *P. aeruginosa*)
  - None represent more than an incremental advance over currently available therapies

Clinical Infectious Diseases 2009;48:1–12

Commonly Used Antibacterials for Serious Infections Are Being Challenged

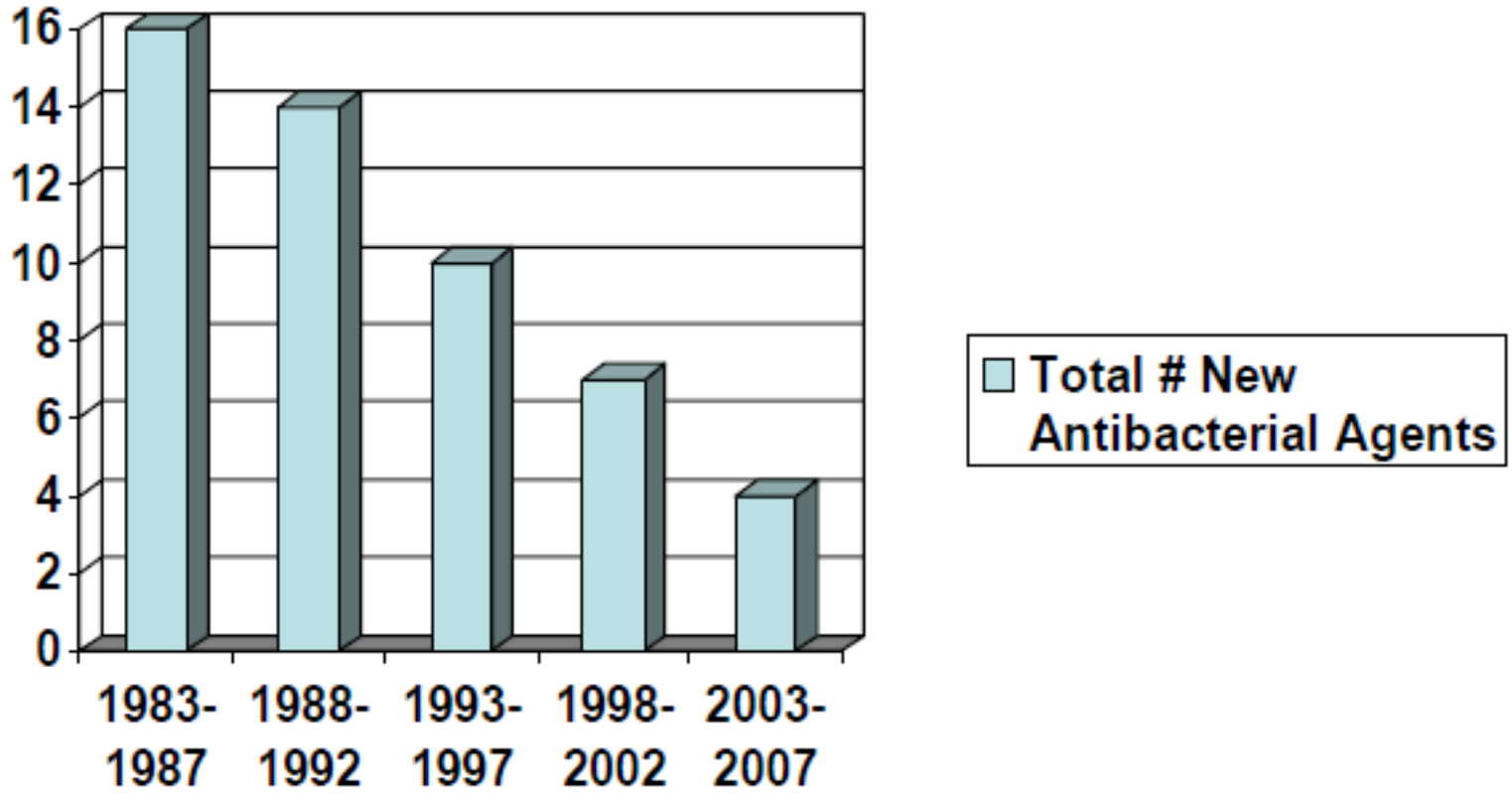
- Days of carbapenem therapy increased 17.4% in a 12-month period ending June 2006



*MAT = moving annual total.

1. Arlington Medical Resources Inc. (AMR) 2006. Total carbapenem days of therapy growth.

Total Approved Antibacterials: US



Spellberg, et. al., *CID* May 1 2004, Modified

Extended-spectrum β-lactamases (ESBLs): The Forgotten (and Underrated) MDR GNB

- Most commonly identified in enterobacteriaceae
- Plasmid-mediated
- Impart decreased susceptibility to β-lactam antimicrobials
  - Often co-resistance to aminoglycosides, fluoroquinolones
- Carbapenems are drugs of choice for invasive infections due to ESBL-producers

CTX-M: ESBL Epidemic

- Common ESBL worldwide, often produced by Escherichia coli
- Often causes UTI
- Now reported in US
  - Healthcare associated
  - Some community
- Community-based ESBL infection raise concern for continued increases in carbapenem use

Urban, Diag Micro Infect Dis, 2010; Sjölund-Karlsson, EID, 2011

The CTX-M Detroit Experience

- From 2006-2011, total number of ESBL-producing E. coli increased from
  - 1.9% of all *E. coli* tested to 13.8% of all E. coli tested
- From 2/11-7/11 at Detroit Medical Center, 575 cases of ESBL-producing *E. coli* were identified
  - 82% urine
  - 8% wound
  - 5% blood
- 491 (85%) were CTX-M producers
- Compared to uninfected controls, unique predictors of CTX-M producing *E. coli* included
  - Prior UTI
  - Nursing home status/impaired functional status
  - Cephalosporin exposure

Hayakawa et al, 2012

Unintended Consequences of Carbapenem Use

Table 1.—Change in Parenteral Cephalosporin and Imipenem/Cilastatin Use From 1995 to 1996 Following Cephalosporin Restriction in 1996

Antibiotics	Year	Unpaired Median Monthly Gram Use (Range)	Change, %	*P*	Paired Median Monthly Gram Use (Range)	*P*
All cephalosporins	1995	5558 (4452 to 8858)	−80.1	<.001	−4709 (−7168 to −3208)	<.001
	1996	1106 (259 to 1690)				
Imipenem	1995	197 (76 to 463)	140.6	<.05	258 (−140 to 551)	.05
	1996	474 (119 to 627)				

Table 4.—Change in Number and Incidence of Patient-Related Imipenem-Resistant *Pseudomonas aeruginosa* From 1995 to 1996 Following Cephalospori Restriction in 1996

Site	Year	No. of PR-IRP	Change, %	Incidence by Unpaired Median PR-IRP/ADC* Ratio (Range)	*P*	Incidence by Paired Median Monthly PR-IRP/ADC Ratio Difference (Range)	*P*
Hospital-wide	1995	67	68.7	0.015 (0.003-0.026)	<.01	0.010 (−0.008-0.031)	<.0
	1996	113		0.025 (0.016-0.042)			

Rahal, JAMA, 1998, 1233-37

Carbapenem Resistance

- Emerging problem in *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Enterobacteriaceae (CRE)
- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care centers (LTACs)
- Severely limits treatment options
  - Increased use of older, toxic agents such as colistin

Klebsiella pneumoniae Carbapenemases (KPCs)

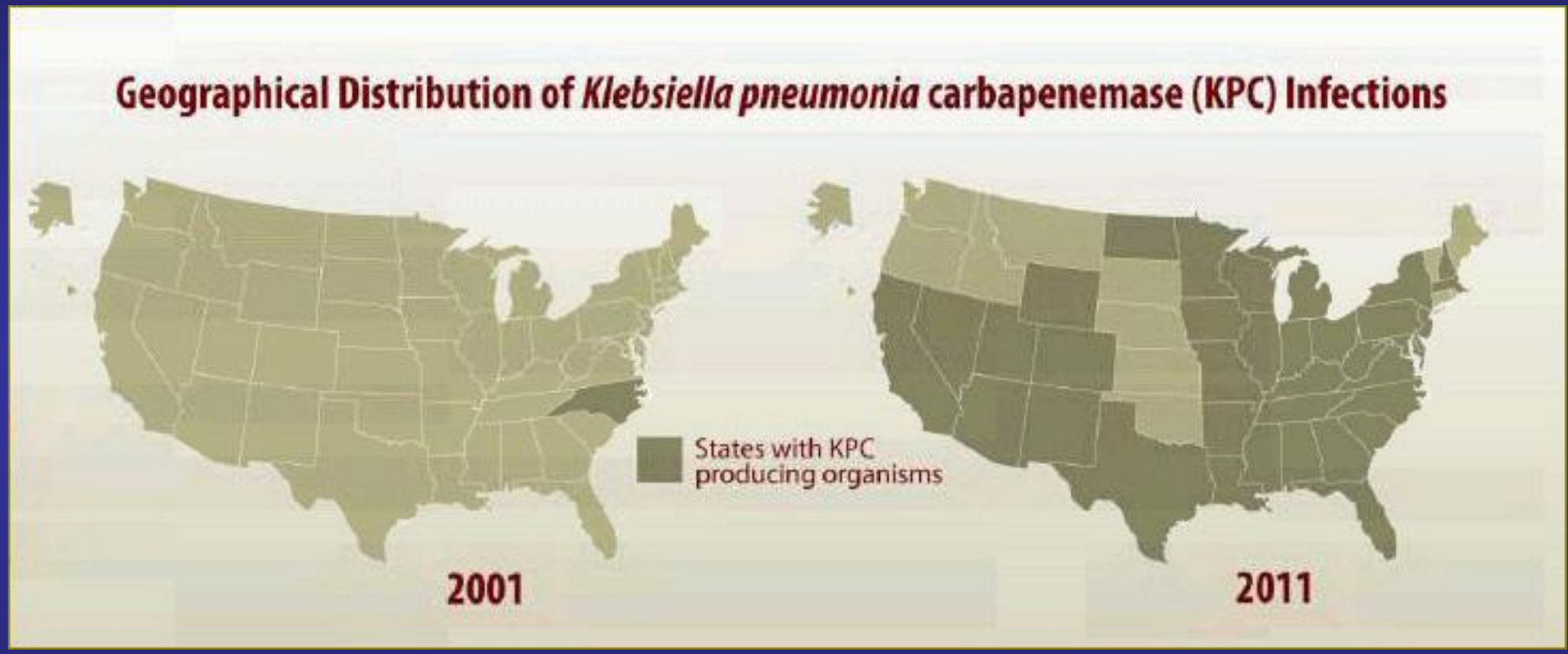
- Plasmid-mediated carbapenemase
- KPC-producing strains of *Klebsiella pneumonia* and other enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
  - Hyperendemicity in NYC
  - 24% of K. pneumoniae infections were due to KPCs in 2 hospitals
- Country-wide outbreak ongoing in Israel, Greece, Columbia and others

*Bratu, AAC, 2005; Quale, CID, 2004; Leavitt, AAC, 2007; Carmeli, Clin Micro Infect, 2010

KPCs (cont)

- Might appear susceptible to imipenem or meropenem, but with borderline MICs per 2009 CLSI breakpoints
  - Usually ertapenem resistant
  - Modified Hodge test
- Usually only susceptible to colistin, tigecycline and select aminoglycosides
- Easily spread in hospitals (often requires cohorting of staff and patients to control)

KPCs in the United States



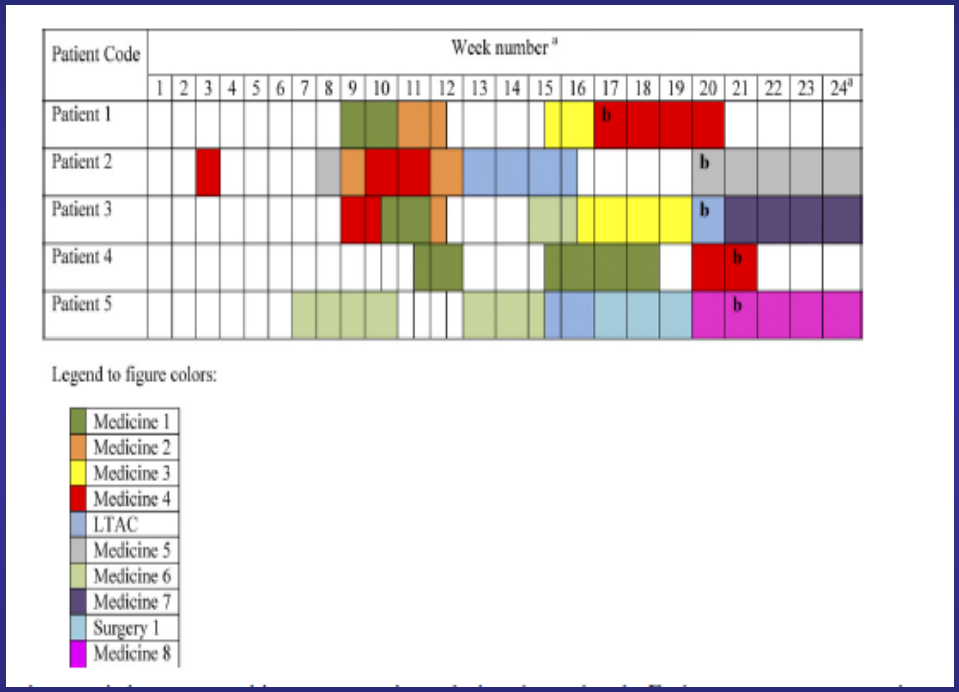
http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/resistance.html

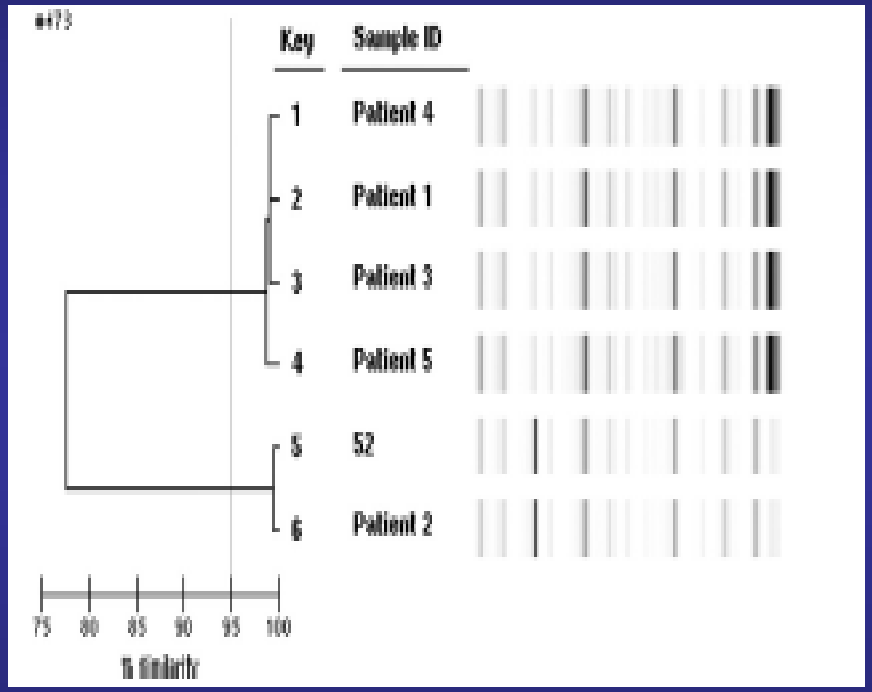
International dissemination of Klebsiella pneumoniae carbapenemase (KPC)–producing Enterobacteriaceae.

Gupta N et al. Clin Infect Dis. 2011;53:60-67

Clinical Infectious Diseases

Outbreak of Colistin-Resistant, Carbapenem-Resistant *Klebsiella pneumoniae* in Metropolitan Detroit, Michigan[▽]





Involved 1 LTAC, 2 hospitals

Marchaim, Antimicrob Agents Chemother, 2011, 593-9

New Delhi metallo-beta-lactamase-1 (NDM-1)

- Carbapenemase mediating broad spectrum resistance
  - Usually found in *Klebsiella pneumonia, E. coli*
- Initially identified in India, Pakistan, Bangladesh
- Recovered in Australia, France, Japan, Kenya, North America, Singapore, Taiwan, and the United Kingdom, Australia, Canada
- Recovered in the US (Massachussetts, Illinois and California)

Tigecycline (Tygacil®)

- Glycylcycline (tetracycline derivative)
- Inhibits protein synthesis by binding to 30s ribosomal subunit
- Broad-spectrum:
  - Active against gram-positive organisms (including MRSA, VRE), gram-negative bacilli (except *Pseudomonas* species) and anaerobes
- IV only: 100 mg followed by 50 mg q 12 hours
  - No renal adjustment necessary
  - Limited serum concentrations
- Major side effects: nausea/vomiting (~20% of patients)
- Limitations
  - Emergence of resistance among GNR during treatment
  - Low serum concentrations – not good option for BSI

Dominguez, Infec Dis Clin Prac, 2009

FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) (9-1-10)

Infection Type	Tygacil deaths/total patients (%)	Comparator Antibiotics deaths/total patients (%)	Risk Difference* (95% Confidence Interval)
cSSSI	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
cIAI	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
CAP	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
HAP	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-VAP	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
VAP	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
RP	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)
DFI	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1, 1.2) **

Limited Antimicrobial Options for Treatment of Extensively Drug-Resistant Gram-Negative bacilli (XDR-GNB)

- Currently available antimicrobials are often not active against XDR-GNB
  - Acinetobacter baumannii non-susceptible to group 2 carbapenems and ampicillin/sulbactam
  - Carbapenem–resistant enterobacteriaciae (CRE)
  - *Peudomonas aeruginosa* resistant to β-lactams, including carbapenems
- With increasing frequency, clinicians are using older agents which are retained in vitro activity
- The polymyxins are one of the most frequently used “old” agents for treatment of XDR-GNB
  - Polymyxin B
  - Polymyxin E (colistin)

New Uses for Old Antibiotics

- “Dry” industry pipeline has led to re-emergence of older drugs for treatment of multi-drug resistant pathogens
- TMP-SMX
- Minocycline
- Fosfomycin
- Rifampin
- Aminoglycosides
- Polymyxins
  - Polymyxin b
  - Polymyxin e (colistin)

Colistin

- Representative agent from polymixin class of antimicrobials
- Unique detergent like mechanisms of action
  - Electrostatic interaction with outer membrane of susceptible bacteria
  - Displacement of divalent cations from the cell membrane
  - Cell membrane integrity disrupted
  - Anti-LPS effect
- No cross-resistance with other classes

Colistin: History

- Originally introduced in 1960's
- High toxicity rates seen
  - Abandoned for less toxic antimicrobials
- Re-introduced in 1990's for treatment of multi drug resistant GNB
- Given as inactive prodrug colistimethate
- Spectrum of activity focuses on problematic Gram-negative organisms
  - Highly active against *P. aeruginosa*, *A. baumannii*, CRE
  - Lacks reliable activity vs *Serratia, Proteus, Providencia*

Colistin – Facts and Challenges

- Never underwent rigorous studies that are required of newer agents
  - Significant pharmacokinetic unknowns from old data
  - Recent publication has improved understanding of pharmacokinetics/dosing
- Multiple products available no conformity in dosing
  - Million units of CMS vs. mg of CMS vs. mg of colistin base activity (CBA)
    - 1 million units CMS equal to 80 mg CMS and 30 mg CBA
  - Product from different manufactures recommend different doses
- Dosing regimens based off inaccurate PK data
  - Non-specific assays

Nephrotoxicity

- Differences in rates of nephrotoxicity[1]
  - Early studies reported high rates (approaching 50%)
  - More recent data reported lower rates
    - Lower doses
- Recent publications reported similar rates of dose-dependent toxicity (~ 40% of all subjects[2-4])

1 Falagas, Critical Care Med, 10, 2006, 1-13; 2 DeRyke, 54, 2010, 4503-5; 3 Hartzell, Clin Infect Diseases, 48, 1724-8; 4 Pogue, CID, 2011, 879-84

Colistin: Clinical Experience

- Data vary greatly and interpretation is difficult
  - Significant delays in effective therapy
  - Patients with many comorbid conditions
  - Varying cocktails of antibiotics used
  - Dosing variable
  - Mono vs combination therapy
  - No randomized controlled studies (ie confounding by indication)
  - Variety of disease states treated

Petrosillo, European Soc Clin Micro Infect Dis, 14, 2008, 816-27

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients▽

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

- NIH-funded pharmacokinetic study in critically ill patients
  - Recommend loading dose of 5mg/kg; cap at 300 mg
  - Maintenance dose equation provided
    - Direct association between renal function and drug concentration
  - No association between weight and colistin levels
    - Applicability to overweight/obese patients unclear
  - Real world application to dosing a patient
    - Assuming a organism MIC of 1 and normal renal function a patient would require ~340 mg/day

Incidence of and Risk Factors for Colistin-Associated Nephrotoxicity in a Large Academic Health System

Jason M. Pogue,[1,2] Jiha Lee,[2] Dror Marchaim,[2,3] Victoria Yee,[2] Jing J. Zhao,[4] Teena Chopra,[2,3] Paul Lephart,[5] and Keith S. Kaye[2,3]

CID 2011:53 (1 November)

Table 3. Colistin Nephrotoxicity as a Function of Dose

Dose (mg/kg IBW)	Nontoxicity, no. (row %)	Toxicity, no. (row %)
≤2.0[a]	8 (89)	1 (11)
2.1–2.9	17 (85)	3 (15)
3.0–3.9	14 (58)	10 (42)
4.0–4.9	17 (77)	5 (23)
5.0–5.9	6 (30)	14 (70)
6.0–6.9	4 (25)	12 (75)
7.0–7.9	4 (40)	6 (60)
≥8.0	2 (40)	3 (60)
<3.0[a]	25 (86)	4 (14)
3.0–4.9	31 (67)	15 (33)
≥5.0	16 (31)	35 (69)

Abbreviation: IBW, ideal body weight.

[a] $P < .001$ for trend.

Levels of colistin necessary to treat some pathogens considered to be susceptible (MIC>1) might not be attainable without inducing high rates of nephrotoxicity (ie might require dose > 5 mg/kg/d)

Randomized Controlled Trial (RCT) for Treatment of Extensively Drug-Resistant (XDR) Gram-negative Bacilli NIH 10-0065

- NIH-funded contract
- Multi-center randomized-controlled double-blind study
  - Anticipate 8 US sites; 1 international site
- Ventilator-associated pneumonia (VAP) and/or bloodstream infection due to XDR-Gram-negative bacilli
  - *Acinetobacter baumannii* non-susceptible to group 2 carbapenems and ampicillin/sulbactam
  - Carbapenem–resistant enterobacteriaciae (CRE)
  - *Peudomonas aeruginosa* resistant to β-lactams including carbapenems

NIH 10-0065 RCT - Treatment arms

- Colistin IV + Imipenem IV vs Colistin IV + placebo IV
- 14 days of treatment (proposed change to 7-14 days)
- Colistin dosing extrapolated from Garonzik et al, 2011
  - Weight considered in dose
  - Ideal body weight (IBW) used; if patient is >130% of IBW then adjusted body weight will be used
  - Loading dose: 5 mg/kg x 1 (max 300 mg)
  - Maintenance dose
    - Clcr ≥ 50 mL/min: 1.67 mg/kg q8h (5 mg/kg/day)
    - Clcr 30 – 49 mL/min: 1.75 mg/kg q12h (3.5 mg/kg/day)
    - Clcr 10 -29 mL/min: 1.25 mg/kg q12h (2.5 mg/kg/day)
    - Clcr < 10 or hemodialysis: 1.5 mg/kg q24h
    - CRRT: full dose
- Imipenem 500 mg or placebo IV q 6 (renally-dosed)

NIH 10-0065 RCT - Outcomes

- Primary: 28-day mortality (all-cause)
- Secondary
  - Clinical improvement
  - Microbiologic cure
  - Emergence of resistant to colistin
  - Adverse events/toxicity
  - Association between colistin serum levels and clinical, microbiologic outcomes, toxicity
  - Association between synergy and clinical, microbiologic outcomes

RCT for XDR- Gram-negative Bacilli : Challenges

- Enrollment and maintenance of subjects
  - Critically ill
  - Competing risks
  - Powers of attorney/patient surrogates
- Prior and concurrent antimicrobial exposures
  - Prior carbapenem exposure
- Timing of enrollment
  - Preliminary microbiology results

Strategies to Control the Spread of MDR GNB

- Contact precautions/hand hygiene
- Environment and source control
- Antibiotic stewardship
- Enhanced infection control measures
- Bundles

Barrier Precautions: Do They Work to Limit the Spread of Multi-Drug Resistant Organisms?

- In outbreak settings, gowns/gloves effective in preventing spread of multidrug-resistant organisms (MDROSs)
- In terms of prevention of endemic spread, data are mostly observational
- Success with many different types of MDROs
  - *Clostridium difficile*
  - Methicillin-resistant *S. aureus* (MRSA)
  - Vancomycin-resistant enterococcus (VRE)
  - MDR Gram-negatives (including carbapenem-resistant enterobacteriaciae (CRE), extended-spectrum B-lactamase-producers (ESBLs), *Acinetobacter baumannii*)

Anderson, Infect Dis Clin N Am 23 (2009) 847–864

Frequency of Contamination of Gowns, Gloves, and Hands of Healthcare Workers (HCWs) after Caring for Patients Colonized or Infected with Specified Bacteria

Source of culture-positive sample	No. (% [95% CI]) of observations	
	Patients with MDR *Acinetobacter baumannii* carriage (n = 199)	Patients with MDR *Pseudomonas aeruginosa* carriage (n = 134)
Gloves	72 (36.2 [29.5–42.9])	9 (6.7 [2.5–11.0])
Gown	22 (11.1 [6.7–15.4])	6 (4.5 [1.0–8.0])
Gloves and/or gown	77 (38.7 [31.9–45.5])	11 (8.2 [3.6–12.9])
Hands[a]	9 (4.5 [1.6–7.4])	1 (0.7 [0–2.2])

Morgan, Infect Control Hosp Epi, 2010, 716-21

Role of the Environment

- Environmental sources of contamination/infection
  - Increasingly recognized as sources of infection
- Particularly important with pathogens such as *Clostridium difficile*, Norovirus, *Acinetobacter* spp.
- Bleach preparations are more effective for some pathogens (still need cleaning)
- Latest technology being tested: UV light, hydrogen peroxide vapor

Environmental cleaning

- Adequacy of cleaning of patients' rooms suboptimal
- Improve monitoring and feedback of efficacy of cleaning
  - Direct observation and culturing not efficient, time-consuming and expensive
- Other options: ATP bioluminescence and fluorescent dyes
  - Monitor process, efficacy of cleaning

Supplements to Routine Environmental Cleaning

- Disinfection units that decontaminate environmental surfaces
- Must remove debris and dirt in order for these units to be effective
- Two most common methods
  - UV light
  - Hydrogen peroxide (HP)

Are Room Decontamination Units Needed to Prevent Transmission of Environmental Pathogens?

William A. Rutala, PhD, MPH;[1] David J. Weber, MD, MPH[1]

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2011, VOL. 32, NO. 8

TABLE 1. Comparison of Room Decontamination Systems That Use UV Irradiation and Hydrogen Peroxide (HP)

	Sterinis	Steris	Bioquell	Tru-D
Abbreviation	DMHP (dry mist HP)	VHP (vaporized HP)	HPV (HP vapor)	UV-C
Active agent	Stenusil (5% HP, <50 ppm silver cations)	Vaprox (35% HP)	35% HP	UV-C irradiation at 254 nm
Application	Aerosol of active solution	Vapor, noncondensing	Vapor, condensing	UV irradiation, direct and reflected
Aeration (removal of active agent from enclosure)	Passive decomposition	Active catalytic conversion	Active catalytic conversion	Not necessary
Sporicidal efficacy	Single cycle does not inactivate *Bacillus atrophaeus* BIs; ~4-$\log_{10}$ reduction in *Clostridium difficile*[a] and incomplete inactivation in situ	Inactivation of *Geobacillus stearothermophilus* BIs	Inactivation of *G. stearothermophilus* BIs; >6-$\log_{10}$ reduction in *C. difficile*[a] in vitro and complete inactivation in situ	1.7–4-$\log_{10}$ reduction in *C. difficile*[a] in situ
Evidence of clinical impact	None published	None published	Significant reduction in the incidence of *C. difficile*	None published

NOTE. Adapted from Otter and Yezli.[18] BIs, biological indicators; VRE, vancomycin-resistant *Enterococcus*.

[a] All *C. difficile* experiments were done with *C. difficile* spores.

Chlorhexidine Gluconate (CHG)

- Broad-spectrum antimicrobial disinfectant
- Preferred agent for skin preparation prior to insertion of vascular catheter and prior to surgery
- Studied for “source control”, decrease in degree of contamination of patients by problem hospital pathogens
  - Reported to reduce risk for carriage and infection with MRSA and VRE

Derde, Intensive Care Med, 2012, 931-9

Prevention of Bloodstream Infections by Use of Daily Chlorhexidine Baths for Patients at a Long-Term Acute Care Hospital

L. Silvia Munoz-Price, MD; Bala Hota, MD, MPH; Alexander Stemer, MD; Robert A. Weinstein, MD

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY NOVEMBER 2009, VOL. 30, NO. 11

- Intervention in LTAC consisted of daily CHG bathing of patients
- 99% reduction in CLABSI by end of intervention period

TABLE 1. Organisms Isolated in Culture of Samples From Patients with Central Venous Catheter–Associated Bloodstream Infection, by Study Period

Variable	Preintervention period (n = 59)	Intervention period (n = 29)	Postintervention period (n = 51)
Pathogen			
CNS	30 (51)	11 (38)	20 (39)
Enterococcus	12 (20)	5 (17)	12 (24)
Candida	9 (15)	6 (21)	3 (6)
Acinetobacter	8 (13)	2 (7)	6 (12)
Pseudomonas	4 (7)	1 (3)	10 (12)
Enterobacter	4 (7)	0 (0)	2 (4)
Corynebacterium	3 (5)	0 (0)	0 (0)
LF GNR	3 (5)	4 (14)	8 (16)
MRSA	0 (0)	1 (3)	7 (14)
Other	2 (3)	0 (0)	0 (0)
No. of pathogens[a]			
1 pathogen	44 (75)	28 (97)	36 (70)
2 pathogens	14 (23)	1 (3)	10 (20)
3 pathogens	1 (2)	0 (0)	5 (10)

NOTE. Data are no. (%) of isolates. CNS, coagulase-negative *Staphylococcus*; LF GNR, lactose fermentor gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*. For descriptions of the 3 different study periods and their interventions, see Methods.

[a] Per blood culture set.

Antimicrobial Stewardship - Goals

- Optimize appropriate use of antimicrobials
  - The right agent, dose, timing, duration, route
- Optimize clinical outcomes
  - Reduce emergence of resistance
  - Limit drug-related adverse events
  - Minimize risk of unintentional consequences
- Help reduce antimicrobial resistance
  - The combination of effective antimicrobial stewardship and infection control has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria
- Strategies for controlling MDR GNB
  - De-escalation, shorter durations of therapy, limiting group 2 carbapenem use

Dellit TH et al. *Clin Infect Dis*. 2007;44(2):159–177; **.** Drew RH. *J Manag Care Pharm*. 2009;15(2 Suppl):S18–S23; Drew RH et al. *Pharmacotherapy*. 2009;29(5):593–607.

Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship

Dror Marchaim, MD;[1] Teena Chopra, MD;[1] Ashish Bhargava, MD;[1] Christopher Bogan, BS;[1] Sorabh Dhar, MD;[1] Kayoko Hayakawa, MD, PhD;[1] Jason M. Pogue, PharmD;[2] Suchitha Bheemreddy, MD;[1] Christopher Blunden, BS;[1] Maryann Shango, MD;[1] Jessie Swan, BS;[1] Paul R. Lephart, PhD;[3] Federico Perez, MD;[4,5] Robert A. Bonomo, MD;[4,5,6,7,8] Keith S. Kaye, MD, MPH[1]

TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

	CRE vs uninfected[b]		ESBL vs uninfected[b]		Susceptible vs uninfected[b]		CRE vs ESBL		CRE vs susceptible		CRE vs all controls combined	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any antibiotic exposure in previous 3 months	11.4 (2–64.3)	.006	1.7 (0.7–4.1)	.24			5.2 (1.4–19.4)	.015	12.3 (3.3–45)	<.001	7.1 (1.9–25.8)	.003
Permanent residency in institution	1.04 (0.2–4.5)	.96	1.3 (0.5–3.6)	.56	0.15 (0.05–0.5)	.002	2.1 (1–4.2)	.05	5.3 (2.1–12.9)	<.001	2.6 (1.3–5.3)	.01
Isolation of resistant bacteria in previous 6 months[c]	15.3 (4.2–55.6)	<001	8.25 (2.7–25.7)	<.001	6.6 (1.9–23.3)	.003	1.7 (0.76–3.7)	.2	1.8 (0.7–4.7)	.23	2.9 (1.4–5.7)	.003
Dependent functional status in background	1.4 (0.5–4.4)	.55	5.6 (2.1–14.7)	.001	2.6 (1.1–6.4)	.03			2.0 (0.7–6.2)	.2	1.6 (0.6–4)	.33
ICU stay in previous 3 months	3.9 (1.3–12.4)	.02	5.2 (2.1–13.2)	.001	3.0 (1.2–7.2)	.02			1.6 (0.6–4)	.34	1.36 (0.7–2.7)	.37
Recent (6 months) invasive procedure	4.2 (1.2–15)	.03	1.2 (0.4–3.4)	.76	3.2 (1.3–8)	.01	2.8 (1.1–7.6)	.04			2.7 (1.1–7.1)	.04
Charlson weighted index comorbidity ≥3	3.1 (0.8–11.8)	.1	1.1 (0.4–2.7)	.87	2.2 (0.94–5)	.07	2.4 (1.03–5.6)	.04	4.8 (1.9–12.5)	.001	3.1 (1.4–7)	.006

NOTE. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

[a] If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

[b] Part of the case-case-control analysis.

[c] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*.

Enhanced Infection Control Processes

- Active Surveillance
- Cohorting of patients
- Dedicated staff
- Bundles

Conclusions

- MDR GNB and CRE are growing in prevalence in multiple geographic locales
- Occur in a variety of healthcare associated settings
  - Even in the community
- Antimicrobial stewardship is here to stay
- Problem is compounded by dry pharmaceutical pipeline
- Novel methods to control spread of MDROs are attractive but not clearly effective/cost-effective

Conclusions (2)

- Technologic advances regarding environmental hygiene are helpful
- Technology and protocols alone will not prevent infections – need compliance with basic process components
- No single process is completely effective in limiting the spread of MDR GNB
  - Bundled interventions have been successful
- More federal dollars geared towards treatment and control of CRE and XDR-GN
- Regional approaches to controlling the spread of antimicrobial resistance are needed
  - Increased CDC and public health involvement